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(54) PURIFIED HUMAN IMMUNOGLOBULIN

(71) SCHWEIZERISCHES SERUM- AND IMPFINSTITUT UND INSTITUT ZUR ERFORSCHUNG DER INFEKTIONSKRANKHEITEN

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(57) Claim

1. Intravenously administrable human immunoglobulin (IgG) for reinforcing the immune defense of the human organism, wherein the immunoglobulin consists of native, chemically unchanged and enzymatically undegraded, stabilized immunoglobulin, which contains no in vitro detectable anti-complementary activity and has an unchanged antibody activity.

3. A method for the preparation of intravenously administrable immunoglobulin for reinforcing the immune defense of the human organism, comprising the steps of: bonding the immunoglobulin obtained by known methods from human plasma or placentas to an ion exchanger, selectively

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ND

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The native immunoglobulin employed as the starting material is used at a protein concentration of 20 to 40 mg/ml

eluting the monomeric immunoglobulin from the ion exchanger, stabilizing the immunoglobulin by treatment with very weak acids or the addition of a polyol, in combination with the addition of a polyglycol and sugar, and removing the last residues of anticomplementary activity by adsorption on aluminum hydroxide.

The IgG aggregates and, moreover, the polymers as

[redacted]

Commissioner of Patents

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91328/82

COMMONWEALTH OF AUSTRALIA

PATENTS ACT, 1952

Form 10
Regulation
13(2)

COMPLETE SPECIFICATION

(ORIGINAL)

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FOR OFFICE USE

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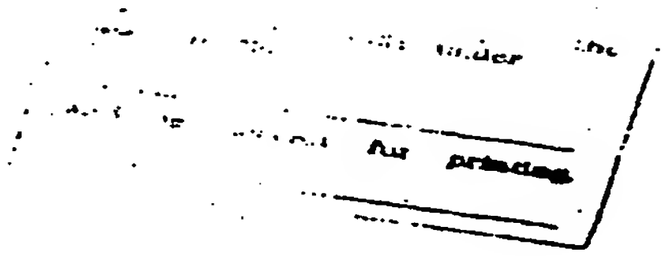

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: SCHWEIZERISCHES SERUM- & IMPFINSTITUT UND INSTITUT ZUR ERFORSCHUNG DER INFEKTIONSKRANKHEITEN

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Complete Specification for the invention entitled: "INTRAVENOUS APPLICABLE HUMAN IMMUNOGLOBULIN AND METHOD FOR ITS PREPARATION"

The following statement is a full description of this invention, including the best method of performing it known to ~~me~~xx us:-

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ASC-49

[redacted]

The third step of the process is indispensible for

Declared at ..... this ..... day of .....

To:

The Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

J. G. STELY

Signature of Declarant(s)

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a new intravenously administrable, native, chemically unchanged and enzymatically undegraded, stable, immunoglobulin, which has no anti-complementary activity, as well as the process for its preparation.

2. Description of the Prior Art

Human immunoglobulins play an important role in the prophylaxis and treatment of infectious diseases and conditions of antibody deficiency. Gamma globulins are used, for example, for the prophylaxis of infections which are of viral origin, such as, hepatitis, measles, German measles, mumps or rabies, or are attributable to bacteria, such as, tetanus, diphtheria, or whooping cough. Gamma globulins are used therapeutically for infections resistant to antibiotics which are caused, for example, by staphylococci, Escherichia coli, Pseudomonas, etc. Specific immunoglobulins (IgG) are also used for the prophylaxis of Rhesus incompatibilities.

Comparison of the anticomplementary activity, [illegible] of commercially available intra-

In addition, the treatment by means of gamma globulins for protection against infections is very important in the case of immune-deficient patients suffering from agammaglobulinemia or hypogammaglobulinemia. Generally, the immunoglobulin is administered intramuscularly. However, this has a number of serious deficiencies as follows:

1) only a limited amount of at most 10 ml can be injected;
2) the resorption by the organism is very delayed (for example, R. Martin du Pan, et al, Blut 5, 104, 1959, have observed that 35 to 40% of the immunoglobulin was still to be found at the injection site after 5 days);
3) a major proportion of the immunoglobulin is broken down by proteolysis at the site of the injection (reference is made, in this connection, to S. Barandun, et al, Vox Sanguinis, 28, 157-175, 1975).

In contrast to this, intravenous injection or infusion leads rapidly to a high level of immunoglobulin in the blood, such as is required, for example, for the treatment of septic-toxic infections. However, an immunoglobulin which is produced by known fractionation processes from blood plasma, serum or placentas, and is suitable for intramuscular application, may not be used for intravenous application. On this subject reference is made to Cohn, et al, J. Amer. Chem. Soc., 68, 459, (1946), A.J.L. Strauss et al, J. Immunol., 93, 24 (1964), A. Horejsi et al, Acta Med. Scand., 155, 65 (1956), and A. Polson et al, Biochem. Biophys. Acta 82, 463 (1964).

TABLE

If such immunoglobulins are administered intravenously, anaphylactoid intolerance reactions occur in about 15 to 30% of the patients (C. A. Janeway et al, New England J. Med. 278, 919 (1968). In the case of immune-deficient patients who require an administration of IgG particularly urgently, the rate of these anaphylactoid intolerances amounts to about 90%.

Up to the present time, there has not been an entirely satisfactory explanation for these reactions. It is known, however, that they are very probably initiated by complement-fixing IgG aggregates which are frequently detectable in conventional, commercial immunoglobulin preparations. This assumption is supported by the fact that a direct relationship was found to exist between the clinical intolerance reactions, the proportion of circulating complement, and the <u>in vitro</u> determined anticomplementary activity of the immunoglobulin. The main objective of the preparation of intravenously administrable immunoglobulins therefore is the removal of their anticomplementary activity (S. Barandun et al, Vox Sanguinis 7, 157-174, 1962).

Several possibilities are presently known for reducing the anticomplementary activity of the immunoglobulins (IgG):

Example 1

Human normal immunoglobulin (IgG, 6 g), which was

The removal of the IgG aggregates by ultracentrifugation or chromatographic separation has been proposed. However, the preparations obtained by these methods are unstable and rapidly become anticomplementary once again, probably as a result of the reaggregation of the monomers (S. Barandun et al, Vox Sanguinis 7, 157, 1962).

According to Austrian patent 359,640, the anticomplementary activity can be reduced by mixing with albumin or serum. The preparations produced according to this process can no longer be described as immunoglobulins since the addition of albumin or serum sufficient for reducing the anticomplementary activity becomes so high that the IgG portion in the total protein mixture becomes too small.

The removal of the IgG aggregates has also been attempted through adsorption by means of activated charcoal (M. Steinbuch, Vox Sanguinis 13, 103, 1967), with starch, with silicates (German Offenlegungsschrift 26 58 334) as well as through precipitation with polyethyleneglycols (German Offenlegungsschrift 27 51 717). None of these methods permits complete removal of the anticomplementary activity.

Preparations without complement-fixing activity are obtained by partial enzymatic break-down of immunoglobulin since proteolytic enzymes, such as, pepsin and plasmin preferentially split off or destroy the Fc segment of the IgG

serum flasks, etc.) so that a 5% protein (IgG) solution is

molecule which contains the complement-fixing domain of this molecule. However, the complete nullification of the biological functions associated with the Fc segment of the IgG molecule, such as, for example, the cytophilic activity, and the opsonization or cytolysis (bacteriolysis) which all require an undamaged Fc segment to which the Fc receptors can bond, is a serious disadvantage of this method. Moreover, the enzymatic splitting of the immunoglobulin molecules results in Fab and $F(ab')_2$ fragments which, while capable of bonding the specific antigens, have only a very short biological half-value time, namely, 18 to 24 hours, instead of 18 to 22 days, as does the complete IgG molecule.

Inspite of these serious disadvantages, several i.v. applicable immunoglobulin preparations which were split with enzymes are on the market:

French patent 2,382,000 describes pepsin-treated products which consist of about 80% $F(ab')_2$ fragments. Only 3 to 5% of the IgG molecules have withstood the proteolysis. These preparations have no anticomplementary activity and the $F(ab')_2$ fragments are capable of neutralizing toxins and viruses.

Plasmin-treated IgG preparations are described, for example, in the German Offenlegungsschrift 27 52 694. They

Example 4

[illegible] IgG which was prepared by the Cohn

contain about 30 to 40% intact IgG (subclasses 2 and 4) which is not split proteolytically. The complement-fixing activity of this preparation is weak (20 to 50 mg/ml/$2CH_{50}$).

According to S. Barandun et al, Vox Sanguinis 7, 157 (1962), the anticomplementary activity of the IgG can be reduced greatly by a 24 hour acid treatment at pH 4 and 37°C. The preparations obtained consist of 85 to 90% of monomeric IgG and 10 to 15% of IgG aggregates. The complement-fixing activity of these products is weak (50 to 70 mg/ml/$2CH_{50}$). Their biological half-value time is, however, reduced to about 14 days and the preparations are not stable during storage and their anticomplementary activity increases once again. A stable, lyophilized preparation produced according to this method has recently been available on the market.

It has also frequently been attempted to obtain intravenously applicable IgG preparations by the action of reactive chemicals using the following methods:

a) The complement receptors of the Fc segment of the IgG are blocked with β-propiolactone. The products so obtained no longer fix any complement and consist of monomers to the extent of 90%. However, the biological half-value time is reduced to 4 to 12 days. For comparison, reference is made to European Patent Application 13,901; S.Barandun et al, Monograph. Allergy, 9, 39-60 (Karger, Basel 1975).

10. anti-rabies antibodies.
11. anti-measles antibodies.

b) Through reduction and sulfonation of the disulfide bridges of the IgG molecule, the anticomplementary activity can also be reduced greatly according to T. Yamanaka et al, Vox Sanguinis 37, 14-20 (1979).

c) Through reduction and alkylation in accordance with a proposal of D.D. Schröder et al, Vox Sanguinis 40, 383-94 (1981) or through amidation in accordance with German Offenlegungsschrift 24 42 655, it is also possible to arrive at intravenously administrable IgG preparations.

Changes in the molecular structure and the appearance of new antigenic determinants in the IgG molecule cannot be excluded by these chemical interventions.

Until now, there has been no ideal immunoglobulin preparation for intravenous administration. The IgG molecules may be modified by enzymatic degradation with loss of properties which depend on the Fc fragment. Alternatively, they are modified by chemical action with changes in the molecular structure, the biological half-value time usually also being reduced. Also, when predominantly physical procedures are employed, a certain residual anticomplementary activity still remains in the IgG preparation.

As indicated heretofore, we have discovered a new intravenously administrable human immunoglobulin (IgG) for reinforcing the immune defense of the human organism, as well as a process for its preparation. The immunoglobulin of the invention is a stable product whose native molecular structure remains unaffected, which retains the original antibody activity and has no <u>in vitro</u> detectable anticomplementary activity. Consequently, it can be administered intravenously without danger, even in the case of particularly endangered immune-deficient patients.

In its process aspect, the present invention comprises a combination of three consecutive, coordinated stages, the anticomplementary activity of the immunoglobulins being reduced in each stage.

The first stage is a basic separation of monomeric immunoglobulin G from its aggregates with the help of an ion exchanger by selectively eluting the IgG monomers, while the IgG aggregates remain bound to the ion exchanger. The eluted monomers fix the complement only weakly, but are very unstable and rapidly become anticomplementary once again, if they are not stabilized. This stabilization is accomplished in the second stage according to the known method of S.I. Miekka et al, Vox Sanguinis 29, 101 (1975) by a weak acid treatment and/or the addition of polyglycols, sugars, and/or polyols, the addition of a polyglycol and a sugar being indispensible. The removal of the last traces of anticomplementary activity is finally accomplished by a third stage composed of a selective adsorption on aluminum hydroxide. The sequence of these three stages is of importance for the performance of the process.

The claims defining the invention are as follows:

The immunoglobulin of the invention no longer exhibits any anticomplementary activity and retains its original molecular structure and also the unchanged antibody activity. It is intravenously administrable to humans for reinforcing the immune defense of the human organism wherein the immunoglobulin consists of native, chemically unchanged and enzymatically undegraded, stabilized immunoglobulin, which contains no in vitro detectable anticomplementary activity and has an unchanged antibody activity.

In the process for the preparation of this intravenously administrable immunoglobulin, immunoglobulin obtained by well-known methods from human plasma or placentas is initially bound to an ion exchanger from which the monomeric immunoglobulin is selectively eluted and then stabilized by treatment with a very weak acid and/or the addition of a

eluting the monomeric immunoglobulin from the ion exchanger, stabilizing the immunoglobulin by treatment with very weak

polyglycol and sugar, and/or of a polyol, the addition of a polyglycol and a sugar being indispensible. The last residues of anticomplementary activity are subsequently removed by adsorption on aluminum hydroxide.

DESCRIPTION OF THE PREFERRED EMBODIMENT

a) More particularly, in the first step of the present invention, an immunoglobulin, isolated by one of the well-known methods is adsorbed on an ion exchanger and the monomeric immunoglobulin is eluted with a 0.02 to 0.2 molar buffer solution at a pH of about 4.0 to 5.5;

b) The largely monomeric eluate is then diafiltered after concentrating or incubating it as a weakly acidic solution with a pH between 4 and 5 at 30 to 45°C for 1/4 to 1 hour, polyglycol, a sugar and, optionally, a polyol being added to the thus stabilized immunoglobulin solution; and then

c) adding an aluminum hydroxide gel, on which the last residues of anticomplementary activity are adsorbed, then removing the adsorbent once again and processing the stabilized immunoglobulin fraction obtained by well-known methods to produce a storable, intravenously injectable form of administering immunoglobulin.

7. A method for the preparation of intravenously administrable immunoglobulin for reinforcing the immune defence

As starting material for the inventive process, an immunoglobulin is used which was obtained from human plasma or human placentas by well-known fractionating procedures, for example, by an ethanol fractionating procedure (Cohn et al), a precipitation procedure with salts (Strauss et al), polyethyleneglycols (Polson et al) or an acridine derivative such as RIVANOL® (Horejsi et al) or by a chromatographic procedure. Placentar immunoglobulin usable as starting material, is obtained, for example, using the method of H. L. Taylor et al, J. Amer. Chem. Soc. 78, 1356 (1956) from the isotonic aqueous placenta extract by fractional precipitation with 95% ethanol.

Immunoglobulin from normal or hyperimmune human plasma or from corresponding placentas can be used as the starting material.

Immunoglobulin with specific antibodies are required for the treatment of infectious diseases and for prophylaxis. For such indications, immunoglobulins are used which were obtained from plasma or placentas which contain antibodies against specific viral or bacterial infections, for example, antiviral antibodies against hepatitis, measles, German measles, mumps or rabies or antibacterial antibodies against tetanus, diphtheria, whooping cough, staphylococci, Escherichia coli, Pseudomonas, etc. Immunoglobulins from plasmas or placentas which contain anti-D (Rho) antibodies are used for the treatment of M[illegible]us hemolytikus neonatorum.

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The native immunoglobulin employed as the starting material is used at a protein concentration of 20 to 40 mg/ml and a a pH of 4.0 to 5.5. For example, a solution of a Cohn fraction II and II, a final precipitate of venous or placentar immunoglobulin or a dissolved lyophilizate or possibly even an ethanol-containing immunoglobulin solution is adjusted by dilution and addition acid to a pH of 4.0 to 5.0. This solution of IgG monomers, IgG dimer, IgG trimers and IgG polymers is separated by means of an ion exchanger (chromatographed).

A cationic exchanger is preferred as the ion exchanger. Especially carboxymethylcellulose (CMC) have proven their value. The ion exchangers are first of all equilibrated with a 0.01 to 0.04 molar buffer solution of a pH of 4.0 to 5.0. Under these conditions, all the immunoglobulin is fixed on the ion exchanger.

As a buffer solution for equilibrating the ion exchanger and diluting the IgG monomers, any biologically safe buffers, such as, for example, acetate buffers, phosphate buffers, citrate buffers or amino acid buffers, can be used. Acetate buffers are preferred. The IgG monomers are used with a 0.02 to 0.2 molar buffer of a pH of 4.0 to 5.5, which additionally contains 0.05 to 0.15 moles common salt.

The IgG aggregates and, moreover, the polymers as well as the trimers and dimers, remain fixed on the ion exchanger and can be eluted later with buffer of higher molarity.

The anticomplementary activity of the monomeric IgG fraction is weak, namely, 60 to 80 mg/ml/$2CH_{50}$, in comparison to that of the starting material (0.3 to 1.0 mg/ml/$2CH_{50}$). The solution of IgG monomers is concentrated and incubated for 1/4 to 1 hour at a pH of preferably 4.1 to 4.6 at 30° to 45°C. The incubation can be omitted if the starting material already has a relatively slight anticomplementary activity.

The immunoglobulin solution is now diafiltered against a buffer solution of pH 5.8 to 6.1, for example, against a 0.005 to 0.015 molar phosphate buffer. Citrate, phthalate and amino acid buffers can also be used for this purpose. For additional stabilization, a polyglycol, a sugar and, optionally, a polyol are added to the IgG solution purified by diafiltration. Preferably, 0.05 to 0.3% (wt/vol) of a polyethylenglycol (PEG 1000 to 6000) or of a polypropyleneglycol are used as polyglycol, 3 to 7% (wt/vol) of saccharose, lactose, maltose or mannose are used as sugar, with saccharose generally being preferred, and 0 to 7% (wt/vol) of sorbitol or mannitol are used as a polyol. The solution obtained is adjusted to a pH of 6.4 to 6.8.

The third step of the process is indispensible for removing the last traces of anticomplementary activity. For this purpose, 5 to 20% (wt/wt) of aluminum hydroxide gel are added to the neutralized IgG solution. The suspension is stirred for 20 minutes to 2 hours at room temperature or overnight at 4°C; it is then centrifuged at 10,000 x g and sterilized by filtering. The filtrate is filled into the final containers, for example, ampoules or serum flasks and subsequently lyophilized.

The immunoglobulin so prepared exhibits the following properties after the lyophilizate is dissolved in distilled water or 0.05 molar salt solution:

1. It no longer contains any measurable anticomplementary activity;
2. The proportion of monomeric immunoglobulin (IgG), determined by gel chromatography, is between 85 and 95%. Fragments are not present;
3. Only a single IgG precipitation line can be seen in immuno-electrophoresis against anti-human antiserum. Decomposition products are not detectable;
4. The distribution of the IgG-subclasses of normal serum is maintained;
5. The activity of the antibody spectrum, based on the protein concentration, remains unchanged.

Comparison of the anticomplementary activity, expressed in mg/ml/$2CH_{50}$, of commercially available intravenously applicable immunoglobulin preparation with that of the inventively obtained natural, unchanged and undecomposed, stabilized immunoglobulin -

The anticomplementary activity is given in mg of protein per ml which are required in order to inhibi two units of complement. It is determined by the 50% hemolysis of sensitized sheep erythrocytes (mg/ml/$2CH_{50}$) according to the standard procedure of M.M. Mayer, Experimental Immunochemistry, 2nd edition, pages 133-240, Charles C. Thomas, Springfield, as well as the procedure of the U.S. Department of Health, Education and Welfare, Public Health Monograph No. 74, "Standardized Diagnostic Complement Fixation Method and Adaptation to Micro Test". The table of results is shown on page 17.

Inventively prepared immunoglobulin preparations are administered intravenously in dosages of 2.5 to 10 g (per dose) to 48 patients. The preparations showed good tolerance in that no unexpected side effects were observed. Only patients, who had no immunodeficiency participated in this preliminary test. On the basis of this experience, a clinical test is justified on patients with inherited or acquired immunodeficiency for whom the vital immunoglobulin therapy is always associated with a certain risk, irrespective of what previous preparation is used.

TABLE

IgG Preparation	Anticomplementary Activity ($mg/ml/2CH_{50}$)
16% standard IgG (for intramuscular application)	0.5 - 1.5
IgG purified by adsorption	3 - 30
IgG treated with β-propiolactone	40 - 50
IgG treated with acids	60 - 80
IgG split or partially broken down with plasmin	20 - 50
IgG split or partially broken down with pepsin	no measurable activity
Inventively prepared IgG (Example 1)	
Starting material	0.7
CMC monomer fraction	60 - 88
IgG preparation after stabilization	150 - 200
End product (Example 1)	no measurable activity

The progress of the inventive preparation and process relative to the state of the art is shown very clearly by the results listed in the Table.

Example 1

Lyophilized immunoglobulin (IgG, 6 g), which was prepared by the known Cohn procedure No. 9 from normal human plasma, is dissolved in 90 ml of distilled water. After a clarifying filtration, the solution is adjusted to a pH of 4.6 with 10% acetic acid and added to a carboxymethylcellulose column (CMC column) (7 cm long, 6 cm in diameter), which was previously equilibrated with 1 l of 0.02 molar acetate buffer of pH 4.6. The IgG is adsorbed on the ion exchanger and the column is washed with 500 ml of the above-mentioned acetate buffer. The monomeric IgG is then eluted with 1.5 L of 0.1 molar acetate buffer of pH 4.6, which contains 8.18 g of sodium chloride per liter and subsequently concentrated with an ultrafilter to 50 ml. This solution which has a protein concentration of 70 to 80 mg/ml is incubated at a pH of 4.1 for 30 minutes at 37°C in a water bath. The pH is gradually adjusted to 5.8 by diafiltration against 1 L phosphate buffer (0 015 M, pH 6.05). In order to stabilize the product, 0.3% (wt/vol) of PEG 4000 and 7% (wt/vol) of saccharose are added. The pH is adjusted to 6.4 with 0.1 N sodium hydroxide. After addition of 10% (wt/wt) of aluminum hydroxide gel, the solution is stirred for 30 minutes at room temperature. The suspension is centrifuged for 20 minutes at 10,000 x g and the supernatant liquid is sterilized by filtration. The preparation is divided into the final containers under sterile conditions and lyophilized. In this procedure, sufficient IgG solution is filled into the final containers (ampoules,

preferentially split off or destroy the Fc segment of the IgG

serum flasks, etc.) so that a 5% protein (IgG) solution is obtained when the lyophilizate is dissolved in doubly distilled water or 0.05 M salt solution, which is suitable for intravenous injection or for infusion.

Example 2

Lyophilized IgG (6g) is dissolved, filtered and purified over CMC by the method described in Example 1. After concentrating the solution, the monomer fraction is dia-filtered directly against 0.015 molar phosphate buffer of a pH of 6.5 until the pH of the solution reaches 5.8, without previously having been treated with acid. After addition of 0.5% PEG 4000 and 3.5% of maltose and 3.5% of mannitol, the pH of the solution is adjusted to 6.4 and the solution is mixed with 10% (wt/wt) of aluminum hydroxide gel. The suspension is stirred for 15 hours at 4°C, centifuged, filtered and processed further as described in Example 1.

Example 3

The final precipitate from the COHN procedure No. 9 which still contains ethanol, is used as the starting material. The precipitate is dissolved in ice cold water and processed further as described in Example 1, the separation however being carried out on the CMC column at 4°C. The remaining operations are carried out as in Example 1. Instead of saccharose, the same amount of lactose is added.

Example 4

Lyophilized IgG, which was prepared by the Cohn procedure No. 9 from human hyperimmune plasma with a higher specific anti-tetanus titer, was used as starting material. At a protein concentration of 10%, the starting material contained 280 I.U. of tetanus/ml. The aqueous solution of this lyophilizate, containing 30 mg of protein per ml, is separated, purified and stabilized according to the 3-step process described in Example 1. The product is free of anticomplementary activity and contains 150 I.U. of tetanus per ml as a 5% protein solution.

Example 5

IgG, containing specific anti-D antibodies (150 mcg/ml in a 10% protein solution) is used as starting material and treated as described in Example 1. The end product contains 85 mcg/ml of specific anti-D antibodies as a 5% IgG solution and is free of anticomplementary activity.

Examples 6 to 12

Intravenous, optimally tolerated preparations, which contain the specific antibodies listed below, are obtained as described in Examples 4 and 5:

6. anti-diphtheria antibodies.
7. anti-hepatitis B antibodies.
8. anti-German measles antibodies.
9. anti-mumps antibodies.

Basel 1975).

10. anti-rabies antibodies.
11. anti-measles antibodies.
12. anti-B. pertussis antibodies.

Based on the protein content, these products retain their high specific antibody activity.

Examples 13 to 22

Immunoglobulin fractions, which were obtained from isotonic, aqueous placenta extracts by precipitation with 95% ethanol, are adjusted to a protein concentration of 30 mg/ml and a pH of 5.0 and separated, purified and stabilized according to the process described in Example 1. The products are free of anticomplementary activity and therefore tolerated optimally intravenously. They contain the antibody spectrum present in the starting material.

13. IgG with a nonspecific antibody spectrum.
14. IgG with anti-German measles antibodies.
15. IgG with anti-tetanus antibodies.
16. IgG with anti-D antibodies.
17. IgG with anti-diphtheria antibodies.
18. IgG with anti-hepatitis antibodies.
19. IgG with anti-mumps antibodies.
20. IgG with anti-rabies antibodies.
21. IgG with anti-measles antibodies.
22. IgG with anti-B. pertussis antibodies.

The claims defining the invention are as follows:

1. Intravenously administrable human immunoglobulin (IgG) for reinforcing the immune defense of the human organism, wherein the immunoglobulin consists of native, chemically unchanged and enzymatically undegraded, stabilized immunoglobulin, which contains no *in vitro* detectable anticomplementary activity and has an unchanged antibody activity.

2. Intravenously administrable human immunoglobulin (IgG) for reinforcing the immune defense of the human organism, wherein the immunoglobulin consists of native, chemically unchanged and enzymatically undegraded, stabilized immunoglobulin, which contains no *in vitro* detectable anticomplementary activity and has an unchanged antibody activity and which contains a nonspecific antibody spectrum or antibodies selected from the group consisting of anti-German measles antibodies, anti-tetanus antibodies, anti-D antibodies, anti-diphtheria antibodies, anti-hepatitis antibodies, anti-mumps antibodies, anti-rabies antibodies, anti-measles antibodies, and anti-B. pertussis antibodies.

3. A method for the preparation of intravenously administrable immunoglobulin for reinforcing the immune defense of the human organism, comprising the steps of: bonding the immunoglobulin obtained by known methods from human plasma or placentas to an ion exchanger, selectively

eluting the monomeric immunoglobulin from the ion exchanger, stabilizing the immunoglobulin by treatment with very weak acids or the addition of a polyol, in combination with the addition of a polyglycol and sugar, and removing the last residues of anticomplementary activity by adsorption on aluminum hydroxide.

4. The method of claim 3 wherein the immunoglobulin used is from normal human plasma or hyperimmune human plasma or from corresponding placentas.

5. The method of claim 4 wherein immunoglobulin is used which contains antibodies against ~~certain~~ specific viral pathogens, bacterial pathogens, or anti-D antibodies.

6. The method of claim 5 wherein the immunoglobulin contains a nonspecific antibody spectrum or antibodies selected from the group consisting of anti-German measles antibodies, anti-tetanus antibodies, anti-D antibodies, anti-diphtheria antibodies, anti-hepatitis antibodies, anti-mumps antibodies, anti-rabies antibodies, anti-measles antibodies, and anti-B. pertussis antibodies.

~~7. Intravenously administrable human immunoglobulin (IgG) as herein described with reference to the given example.~~

7. A method for the preparation of intravenously administrable immunoglobulin for reinforcing the immune defence of the human organism as herein described with reference to the given examples.

DATED this 7th day of December, 1982

SCHWEIZERISCHES SERUM- & IMPFINSTITUT UND INSTITUT ZUR ERFORSCHUNG DER INFEKTIONSKRANKHEITEN

By Their Patent Attorneys,

ARTHUR S. CAVE & CO.